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Circulating tumor DNA (ctDNA) in precision oncology of ovarian cancer

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Circulating tumor DNA (ctDNA) is short, typically <167 base pairs long DNA fragments[1] in body fluids, for example, serum and plasma fractions of bloodstream. While mechanisms for ctDNA release are currently poorly understood, a number of articles report good congruence between the mutations and copy-number alterations (75%-100%)[2–4] identified from ctDNA and representative tissue biopsy. As ctDNA sampling is minimally invasive, ctDNA reflects better cancer heterogeneity in a patient than a tumor biopsy[5], and in solid tumor cancers often the only option to query genomic landscape of relapsed disease and metastases, it has been welcomed as a basis for precision oncology approaches.

Utility of ctDNA has been well documented in early detection of cancer[4, 6], prognosis[7–9], and treatment monitoring[10, 11]. In CancerSEEK study, 43% of stage I cancers were detected from ctDNA[4] and in general, 70% of cancers were detectable from ctDNA. CtDNA has also been used to detect possible residual disease after primary treatment to identify patients with poor prognosis[8]. Overall, treatment response monitoring through ctDNA allele frequencies is widely adaptable[11]. However, evidence for the use of ctDNA in guiding treatment decisions currently is scarcer[12]. In this editorial we focus on the use of ctDNA in precision oncology in guiding treatments of patients with solid tumor cancers.

ctDNA is used in guiding treatments for non-small cell lung cancer, where EGFR tyrosine kinase inhibitors (TIKs) are given based on *EGFR* mutations[13]. Currently, the lung cancer ctDNA test is the only FDA approved test for ctDNA-guided treatment. CtDNA is also used for colorectal cancer to target anti-EGFR treatments to specific patients through *EGFR* and *KRAS* mutations[12]. In other cancers, ctDNA has been used to guide treatment based on mutations in multiple different genes for example in gastric cancer[14, 15], colorectal cancer[16] and pancancer settings [17–19] with positive impact on survival.

We recently published a paper on the use of ctDNA in management of high-grade serous ovarian cancer (HGSOC)[2]. HGSOC is the most frequent and lethal subtype of epithelial ovarian cancer with five-year survival of only 43%. Most patients respond to primary therapy, consisting platinum-based chemotherapy and debulking surgery, but eventually relapse with limited treatment options. All HGSOC patients have *TP53* driver mutation, and tumors are characterized by large molecular heterogeneity and abundant copy-number changes. We used targeted sequencing panel of over 600 cancer-related genes and longitudinal sampling to genetically profile 12 patients. In seven patients, actionable targetable mutations and copy-number alterations were identified. For one of them, treatment was changed to include trastuzumab based on the revealed *ERBB2* amplification, which resulted in a rapid and dramatic clinical response.

In ovarian cancer, treatment response and detection of relapse are commonly tracked through CA-125 through blood. Even with available detection method, ctDNA has shown to detect treatment response more sensitively and relapse earlier than CA-125[20, 21]. The tumor burden analyses are based on truncal *TP53* mutation allelic frequencies in plasma. The early detection of relapse in

combination with timely molecular profiling would allow to treat ovarian cancer patients more efficiently.

The main reasons for a relative small number of cases where ctDNA has been used in guiding treatment decisions are as follows. Firstly, the quality of bioinformatics pipelines for ctDNA data analysis has been variable and often poorly documented. Secondly, low amount of ctDNA makes it difficult to obtain enough information and differentiate true signal from noise[22]. Thirdly, timeframe to provide information from ctDNA has been too long to provide timely information to treat patients at the clinic. Lastly, focus has been only on single mutations. It has worked in some cancers, like *EGFR* mutant lung cancer, but suffers from the heterogeneity between and within patients or possible reversion events.

All the above issues are solvable. Bioinformatics community has responded to the need for open, tailored ctDNA pipelines and several pipelines have been published[1, 2]. These new public pipelines for variant calling and filtering enable development of state-of-the-art methods and enable reliable comparisons between studies which may enlighten some of the differences detected earlier[23]. Better protocols for data analysis ensure maximum sensitivity and specificity from the provided sequencing data. Simultaneous development of more sensitive sequencing techniques[8] enable the detection of lower amounts of ctDNA. Especially the sequencing of early stage cancers and post-surgical minimal residual disease depend on detection of extremely low amounts of ctDNA. New detection techniques have significantly improved the detection limits and there are protocols suitable for detection of low amount of ctDNA in residual disease, as low as 0.0003 allele fractions[8]. The detection limits for larger panels and other than patient-specific mutations are still higher but ongoing efforts are made to overcome the issue also in these assays. Maturation of the protocols has also improved the timeline from sample extraction to passing of clinically relevant information back into the clinics.

Many ctDNA assays provide information on individual mutations, copy-number alterations, or DNA methylations to guide treatment. In studies, where ctDNA-guided matched treatment has been used, not all patients are identified with targetable mutations. A partial explanation is the low number of covered genes and/or low sensitivity. Larger panels exist to detect more rigorous molecular profile and further information on other genetic variation altering the mutation-related response are already being used[18]. When knowledge on molecular variants affecting drug response continue to accumulate, it will be possible to identify more significant, clinically relevant alterations in larger numbers of cancer patients.

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